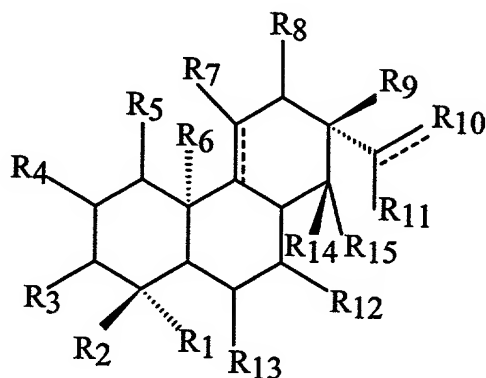


NOVEL INTERLEUKIN-1 AND TUMOR NECROSIS FACTOR- α MODULATORS, SYNTHESIS OF SAID MODULATORS AND METHODS OF USING SAID MODULATORS

Abstract of the Disclosure

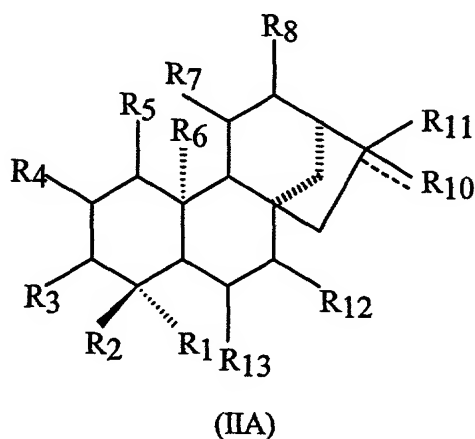
Novel compounds are disclosed that have the chemical structure of Formula (II), and its prodrug esters and acid-addition salts, and that are useful as Interleukin-1 and Tumor Necrosis Factor- α modulators, and thus are useful in the treatment of various diseases.



(II)

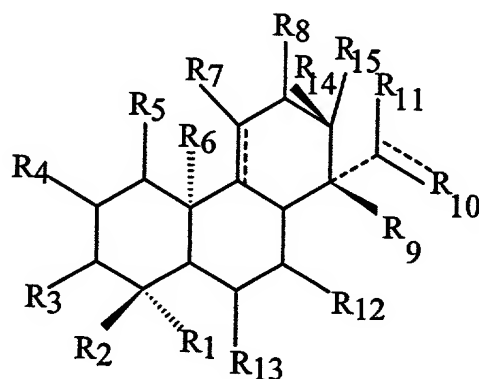
wherein the R groups are defined as follows: if any R₃-R₅, R₇, R₈, R₁₁-R₁₃ is not hydrogen, R₂ or R₆ or R₉ is not methyl, or R₁₀ is not CH₂, then R₁ is selected from the group consisting of hydrogen, a halogen, COOH, C₁-C₁₂ carboxylic acids, C₁-C₁₂ acyl halides, C₁-C₁₂ acyl residues, C₁-C₁₂ esters, C₁-C₁₂ secondary amides, (C₁-C₁₂)(C₁-C₁₂) tertiary amides, C₁-C₁₂ alcohols, (C₁-C₁₂)(C₁-C₁₂) ethers, C₁-C₁₂ alkyls, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyls, C₂-C₁₂ substituted alkenyls, and C₅-C₁₂ aryls. If all R₃-R₅, R₇, R₈, R₁₁-R₁₃ are hydrogen, R₂, R₆, and R₉ are each methyl, and R₁₀ is CH₂, then R₁ is selected from hydrogen, a halogen, C₁-C₁₂ carboxylic acids, C₁-C₁₂ acyl halides, C₁-C₁₂ acyl residues, C₂-C₁₂ esters, C₂-C₁₂ secondary amides, (C₁-C₁₂)(C₁-C₁₂) tertiary amides, C₂-C₁₂ alcohols, (C₁-C₁₂)(C₁-C₁₂) ethers other than methyl-acetyl ether, C₂-C₁₂ alkyls, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyls, C₂-C₁₂ substituted alkenyls, and C₂-C₁₂ aryls. R₂ and R₉ are each separately selected from hydrogen, a halogen, C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ acyl, C₁-C₁₂ alcohol, and C₅-C₁₂ aryl. R₃-R₅, R₇, R₈, and R₁₁-R₁₃

are each separately selected from hydrogen, a halogen, C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ alkynyl, and C₅-C₁₂ aryl. R₆ is selected from hydrogen, a halogen, C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyl, C₂-C₁₂ substituted alkenyl, and C₂-C₁₂ alkynyl. R₁₀ is selected from hydrogen, a halogen, CH₂, C₁-C₆ alkyl, C₁-C₆ substituted alkyl, C₂-C₆ alkenyl, C₂-C₆ substituted alkenyl, C₁-C₁₂ alcohol, and C₅-C₁₂ aryl. Furthermore, novel compounds that have the chemical structure of Formula (IIA) and its prodrug esters and acid-addition salts are disclosed, and that are useful as Interleukin-1 and Tumor Necrosis Factor- α modulators, and thus are useful in the treatment of various diseases..



wherein the R groups are defined as follows: If any R₃-R₅, R₇, R₈, R₁₁-R₁₃ is not hydrogen, R₂ or R₆ is not methyl, R₁₀ is not CH₂, or if it is not true that R₁₀ is CH₂OH and R₁₁ is OH, then R₁ is selected from the group consisting of hydrogen, a halogen, COOH, C₁-C₁₂ carboxylic acids, C₁-C₁₂ acyl halides, C₁-C₁₂ acyl residues, C₁-C₁₂ esters, C₁-C₁₂ secondary amides, (C₁-C₁₂)(C₁-C₁₂) tertiary amides, C₁-C₁₂ alcohols, (C₁-C₁₂)(C₁-C₁₂) ethers, C₁-C₁₂ alkyls, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyls, C₂-C₁₂ substituted alkenyls. However, if all R₃-R₅, R₇, R₈, R₁₁-R₁₃ are hydrogen, R₂ and R₆ are each methyl, and R₁₀ is CH₂ or CH₂OH, then R₁ is selected from hydrogen, a halogen, C₁-C₁₂ carboxylic acids, C₁-C₁₂ acyl halides, C₁-C₁₂ acyl residues, C₂-C₁₂ esters, C₁-C₁₂ secondary amides, (C₁-C₁₂)(C₁-C₁₂) tertiary amides, C₂-C₁₂ alcohols, (C₁-C₁₂)(C₁-C₁₂) ethers, C₂-C₁₂ alkyls, C₂-C₁₂ substituted alkyls, C₂-C₁₂ alkenyl, and C₂-C₁₂ substituted alkenyl. R₂ is selected from hydrogen, a halogen, C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ alkynyl, and C₁-C₁₂ acyl, and C₅-C₁₂ aryl. R₃, R₄, R₅, R₇, R₈, and R₁₁-R₁₃ are each separately

selected from hydrogen, a halogen, C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ alkynyl, and C₅-C₁₂ aryl. R₆ is selected from hydrogen, a halogen, C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyl, C₂-C₁₂ substituted alkenyl, and C₂-C₁₂ alkynyl. R₁₀ is selected from hydrogen, a halogen, CH₂, C₁-C₆ alkyl, C₁-C₆ substituted alkyl, C₂-C₆ alkenyl, C₂-C₆ substituted alkenyl, C₁-C₁₂ alcohol, and C₅-C₁₂ aryl. Pharmaceutical compositions comprising a therapeutically effective amount of acanthoic acid or of the compounds of Formula (II) and Formula (IIA), and a pharmaceutically acceptable carrier, are also disclosed, and are useful as anti-inflammatory analgesics, in treating immune disorders, as anti-cancer and anti-tumor agents, and in the treatment of cardiovascular disease, skin redness, diabetes, transplant rejection, otitis media, sinusitis, and viral infection. Furthermore, novel compounds that have the chemical structure of Formula (IIB) and its prodrug esters and acid-addition salts are disclosed, and are useful as Interleukin-1 and Tumor Necrosis Factor- α modulators, and thus are useful in the treatment of various diseases.



(IIB)

wherein the R groups include the following: R₁ is selected from the group consisting of hydrogen, a halogen, COOH, C₁-C₁₂ carboxylic acids, C₁-C₁₂ acyl halides, C₁-C₁₂ acyl residues, C₁-C₁₂ esters, C₁-C₁₂ secondary amides, (C₁-C₁₂)(C₁-C₁₂) tertiary amides, C₁-C₁₂ alcohols, (C₁-C₁₂)(C₁-C₁₂) ethers, C₁-C₁₂ alkyls, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyls, C₂-C₁₂ substituted alkenyls; R₂ is selected from hydrogen, a halogen, C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ alkynyl, and C₁-C₁₂ acyl, and C₅-C₁₂ aryl. R₃, R₄, R₅, R₇, R₈, and R₁₁-R₁₃ are each separately selected from hydrogen, a halogen, C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ alkynyl, and C₅-C₁₂ aryl. R₆ is

selected from hydrogen, a halogen, C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyls, C₂-C₁₂ alkenyl, C₂-C₁₂ substituted alkenyl, and C₂-C₁₂ alkynyl. R₁₀ is selected from hydrogen, a halogen, CH₂, C₁-C₆ alkyl, C₁-C₆ substituted alkyl, C₂-C₆ alkenyl, C₂-C₆ substituted alkenyl, C₁-C₁₂ alcohol, and C₅-C₁₂ aryl. The disclosed compounds include the prodrug esters of the above compounds, and the acid-addition salts thereof. The disclosed compounds include the prodrug esters of the above compounds, and the acid-addition salts thereof. Pharmaceutical compositions comprising a therapeutically effective amount of the novel compounds of Formulae (II) and (IIA), and their prodrug esters, and a pharmaceutically acceptable carrier, are also disclosed, and are useful as anti-inflammatory analgesics, in treating immune disorders, as anti-cancer and anti-tumor agents, and in the treatment of cardiovascular disease, skin redness, and viral infection. Completely synthetic and semi-synthetic methods of making the compounds of Formulae (I) and (II), and their analogs, and the compounds of Formulae (II), (IIA) and (IIB) are disclosed, as are methods of using these synthetic and semi-synthetic compounds in the treatment of the above-listed disease states.

S:\DOCS\JMR\JMR-4849.DOC 011102